Improving drug regimens and implementation strategies for malaria prevention in pregnant women in western Kenya
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Chapter 8: Discussion and Conclusions
Discussion and Conclusions

Despite being a treatable and preventable disease, malaria still causes nearly 800,000 deaths and exacts a heavy toll on approximately 125 million women who become pregnant in malaria endemic areas annually (WHO, 2008; Dellicour et al, 2010). As discussed in chapter 1, malaria endemic countries rely on a multipronged approach of using prompt diagnosis and treatment (most recently highly efficacious ACTs), IPTp, ITNs and targeted IRS. The combined effects of these strategies have been shown to effectively bring down the burden of malaria but their effectiveness is hampered by the rapid development of *P. falciparum* resistance to SP, drug interactions such as between SP and folate, insufficient knowledge of pharmacokinetics and dynamics of antimalarial drugs in pregnant women and children, leading to sub-optimal treatment, and operational challenges leading to low coverage. This discussion is structured on three main themes, which include main findings of the studies described in this thesis, lessons learnt, implications for public health policy, priority areas for research and future strategies in the face of changing malaria epidemiology.

Burden of malaria and anaemia

*Lessons learnt and conclusions*

First we determined the prevalence of malaria, anaemia and associated risk factors among first ANC attendees in western Kenya (chapter 2). We showed that malaria and anaemia are already established problems in pregnant women by the time they come for first antenatal clinic visit (malaria being present in 1 out of 5 women, and anaemia in 7 out of 10 women). Further, we showed that important risk factors for malaria were factors related to exposure such as type of housing construction, peri-urban residence and a recent visit to a rural setting. Importantly, the use of an ITN was associated with a reduced risk of malaria infection and anaemia. It has been proposed that severe maternal anaemia (Hb < 7 g/dl) has the potential to be used for monitoring the effectiveness of malaria control in pregnancy (Savage et al, 2007; Brabin et al, 2008). If this approach is adopted for routine evaluation of malaria control measures in our setting, our data provides an important benchmark for future evaluations. Importantly, our data provides policymakers with the information needed for appropriate timing of season or trimester to apply intervention strategies for optimal benefits. Of the two malaria prevention strategies IPTp cannot
be started until after quickening. Therefore we propose an earlier start with ITNs and iron and folate supplementation, even before pregnancy.

**Folic acid, high dose folic acid, high physiological folic acid concentrations and efficacy of sulfadoxine-pyrimethamine**

*Lessons learnt and conclusions*

In chapters 3 and 4 we showed that folic acid supplementation in a high dose (5mg daily) reduced the efficacy of SP in clearing peripheral malaria parasitaemia. Folic acid supplementation around conception and early in pregnancy is effective in protecting against neural tube (spine and brain) defects and continued supplementation around pregnancy prevents anaemia in the mother. However, folic acid synthesis by the malaria parasite is also the target of antifolate anti-malarial drugs such as SP. Previous studies had shown that folate antagonizes SP *in vitro* and *in vivo* and results from other studies suggested that high dose folate can reduce the efficacy of SP in children and in adults (Dzinjalama et al, 2005; van Hensbroek et al,1995; Nzila et al, 2006; Carter et al, 2005). Unfortunately, these studies did not examine the effect of high dose folate in pregnant women, for whom most national bodies recommend regular folate supplementation. Our data adds to this growing body of evidence.

Additionally, measurement of physiologic folate from the blood taken from these women just before supplementation (*chapter 4*) confirmed that high folic acid level was the most consistent risk factor across all time points, even when we controlled for other biological factors. Our findings that plasma folate levels markedly reduce the efficacy of SP provides further support for our previous observation that high dose (5 mg/day) folate supplementation should be avoided in pregnant women who are receiving SP for prevention or treatment of malaria (*chapter 4*). In the light of these findings with SP, and the results from our retrospective study assessing the effectiveness of daily cotrimoxazole (CTX) on the prevention of malaria in pregnant women (chapter 5), we hypothesize that high dose folic acid could also reduce the efficacy of CTX, an antifolate with similar mode of action, which is also the standard of care for preventing opportunistic infections in HIV-infected individuals, including pregnant women.

Furthermore this study showed that folate deficiency was rare and women with higher physiologic folate levels were likely to fail treatment, indirectly suggesting that folate supplementation may not be justified in this setting.
Our study had important policy implications. We suggest that countries currently using SP for treatment or prevention of malaria in pregnancy need to re-evaluate their antenatal policy on timing or dosage of folic acid supplementation to optimize SP efficacy. In the former, the internationally recommended dosage of 0.4-0.6 mg/day should be adhered to. In a series of discussions with the Kenyan Ministry of Health’s Divisions of Malaria Control and Division of Reproductive health, the policy has in principle been changed to using 0.6 mg folic acid/day at the ANC.

The effectiveness of cotrimoxazole for malaria prevention in HIV-infected pregnant women

Lessons learnt and implications for policy

In chapter 5 we evaluated whether daily cotrimoxazole prophylaxis given to pregnant HIV-infected women for prevention of opportunistic infections adequately prevents placental malaria. WHO and the Kenyan Ministry of Health recommend that pregnant HIV-infected women receiving cotrimoxazole prophylaxis should not be given IPTp-SP. The effectiveness of CTX to prevent or treat malaria has been documented (Hamel at el, 2008) and CTX has been shown to reduce the burden of clinical malaria in HIV-infected adults (Mermin et al, 2006). However, no studies had addressed whether CTX given once daily would prevent placental malaria. In chapter 5 we showed that CTX prophylaxis resulted in reduced prevalence of placental parasitemia, peripheral parasitaemia as well as other adverse birth outcomes compared to HIV-negative women receiving IPTp-SP. Our results were consistent with those of other recent studies in pregnancy. A cross sectional study assessing the prevalence of placental malaria among HIV-infected and uninfected women receiving anti-folates in a high transmission area of Uganda showed that the prevalence was similar in HIV-infected women taking CTX and HIV-uninfected women on IPT-SP (Newman et al, 2009). A more recent study in Malawi showed that in pregnant women, daily CTX was associated with reduced malaria parasitaemia, and anaemia compared with IPTp-SP (Kapito-Tembo et al, 2011).

Our study had important policy implications because it validates the current WHO and Kenyan Ministry of Health policy for malaria prevention in pregnant HIV-infected women and provides a scientific basis for reliance on CTX for malaria prevention in this subgroup.

Although daily CTX was associated with a low prevalence of placental parasitemia this may at least in part be related to declining transmission in the study area. In the light of our
current findings, the recommendation for use and adherence to CTX during pregnancy for HIV-infected women should be re-emphasized together with efforts aimed at evaluating additional strategies to further reduce the prevalence of placental parasitemia in this sub-group. Already trials are ongoing to assess the added benefit of mefloquine to HIV-infected women on CTX who are also using ITNs (http://www.mip-consortium.org/).

Low coverage with sulfadoxine-pyrimethamine and low utilization of crucial services despite high ANC attendance

Lessons learnt and implications for policy

In chapter 6 and 7 we examined the status of implementation of IPTp and other ANC services and attempted to identify barriers to effective implementation of these strategies in rural western Kenya. In a cross-sectional survey of 830 women, we assessed the effect of re-training health care providers on the use of IPTp. The evaluation was done 2 years after re-training the ANC staff on focused antenatal care/malaria in pregnancy (FANC/MIP) and showed an overall increase of IPTp use from 7% in 2002 to 21% in 2005. The increase in IPTp use was greater in Asembo (the area where FANC/MIP training was conducted) compared to areas with no training. These results are consistent with other surveys in Kenya which showed surprisingly low coverage (DHS Kenya, 2003; van Eijk et al, 2005; Guyatt et al, 2004; Gikandi et al, 2008; Kenya Malaria Indicator Survey, 2010) and did not reach the 60% target set at Abuja (WHO, 2000) or the more ambitious recent RBM targets (RBM, 2008). This being an important process indicator that can be used to monitor and improve malaria control programmes in Africa, the World Health Organization in consultation with African heads of state set benchmark targets that needed to be achieved by the year 2005 (WHO, 2000). The target set for IPTp was that, “at least 60% of all pregnant women, who are at risk of malaria, especially those in their first pregnancies, should have access to chemoprophylaxis or intermittent preventive treatment” (WHO, 2000). Although most malaria endemic countries adopted IPTp policy, coverage remains low. Probable operational challenges include inequitable access to ANC services, payment policies for IPTp, health care worker skills and beliefs, staff shortages at antenatal clinics, drug shortages, not providing SP directly observed, lack of demand for ANC, perceptions of drug safety and late antenatal attendance (Hill et al, 2006). But even where health infrastructure is good and commodities are available, performance has been sub-optimal. The observed low IPTp coverage
in a setting of high ANC attendance and the apparent availability of SP in the clinics demonstrates considerable missed opportunity as women actually visit the ANC and do not receive IPTp.

The main lesson learnt is that the rates at which research findings are translated into policy and practice remains disturbingly slow. This low coverage has been observed in many countries and remains an important impediment to the implementation of proven and efficacious tools for malaria prevention (Guerin et al, 2002; Hill & Kazembe, 2006; Greenwood et al, 2007; van Eijk et al, 2011).

Among other things we identified health worker confusion surrounding the appropriate timing of IPTp as the main hindrance to the optimal coverage with IPTp despite the fact that IPTp policy had been in force for a long time. Our model for increasing IPTp uptake used a simplified version of the policy document (an easy to read memo or job aid). The success of this approach showed that giving targeted simplified instructions to health care providers had the potential to increase IPTp uptake (Ouma et al, poster no. LB.2264, American Society of Tropical Medicine and Hygiene, 59th Meeting, Atlanta, GA, 2010). We concluded that refresher training and use of simplified messages may be a key strategy in achieving the Roll Back Malaria targets for malaria prevention in pregnancy in Kenya, currently set at 80%.

These results have now been assimilated into policy by the Kenyan Ministry of Health (See sample memo in appendix 1). Consistent with its current epidemiological map Kenya has recently reviewed its policy for provision of IPTp to re-focus more in malaria endemic regions of Nyanza, Western and Coast provinces and is employing this “memo” approach as its key implementation strategy. Since factors that hinder the attainment of IPTp targets are similar in many areas, the results of this study can be replicated in other malaria endemic countries in Africa.

**Current challenges to Malaria in Pregnancy control**

*IPTp with sulfadoxine pyrimethamine*

The development of resistance to SP, the only anti-malarial drug currently recommended for IPTp, remains one of the most important challenges facing malaria prevention in pregnant women in our setting. Until recently SP has been widely used as first line therapy for uncomplicated *P. falciparum* malaria in sub-Saharan Africa but increase in resistance has
become a major concern (McCollum et al, 2006). Anti-malarial drug resistance is known to shorten the period of post-treatment prophylaxis thereby leaving women unprotected for longer duration (White et al, 2008). The widespread rise of antifolate resistance has been markedly high in East and Central Africa. In western Kenya SP treatment failure rates had reached 56% in children (Obonyo et al, 2007) and 37% in pregnant women (Ouma et al, 2006). This substantial decrease in the efficacy of SP raised concerns about the future of the IPTp-SP strategy. In view of these concerns a systematic review of data published between 1996 and 2006 was conducted to assess the effect of SP resistance on the efficacy of IPTp for malaria control during pregnancy (ter Kuile et al, 2007). The results showed that in areas in which 1 of 4 treatments with SP fail in children by day 14 and about 40% by day 28, the 2-dose IPTp with SP regimen continues to provide substantial benefit to HIV-negative semi-immune pregnant women. However, more frequent dosing is required in HIV-positive women not using cotrimoxazole. These results were encouraging, and seemed to give room or at least a temporary respite until an alternative is developed.

A more recent study in an area of Tanzania with very high SP resistance showed that IPTp use was associated with an increased fraction of parasite resistance alleles at DHPS codon 581, an increase in the level of parasitemia and more intense placental inflammation suggesting that the use of partially effective anti-malarial agents for IPTp may exacerbate malaria infections in the setting of widespread drug resistance (Harrington et al, 2009) and more data from the same area has further demonstrated that IPTp-SP does not improve pregnancy outcomes in conditions where SP-resistant parasites predominate and may even increase the odds of foetal anaemia; they concluded that the overall effect of IPTp may transition from net benefit to neutral or net harm (Harrington et al, 2011). However, net harm has not been identified in other studies in areas of high SP resistance where no additional mutation in DPHS codon511 is still rare including our study area of western Kenya.

The threshold of resistance at which IPTp with SP ceases to be useful as a strategy for malaria prevention in pregnancy has been identified as a priority area of research (WHO, 2007). Currently studies are being conducted in at least 8 sites in Africa to determine the relationship between the degree of SP resistance in the population as assessed by molecular markers and the ability of IPTp-SP to clear existing infections in asymptomatic women attending ANC and to prevent placental malaria and the adverse effects of malaria at delivery (in vivo IPTp-Monitoring...
studies). Our site is participating in these trials and the results will inform decisions regarding the future of IPTp-SP strategy.

**Dose optimization**

Currently WHO recommends that HIV negative women receive “at least 2 doses of IPTp-SP” one in the second trimester and another in the third trimester (WHO, 2000). However, the question that is frequently asked is whether 2 doses of SP are enough. The disadvantage of the 2-dose regime is that women get their second dose early, leaving them unprotected for about 6-8 weeks in the later part of their pregnancy, with the risk of malaria infection at an important period for foetal growth. Most malaria endemic countries in Africa use the 2-dose regimen while only a few countries (Malawi, Ghana and Zambia) use the 3-dose regimen (with an interval of 1 month between doses) (van Eijk et al, 2011) and Malawi and Kenya have revised their strategy from 2-dose regimen to recommending SP at each monthly ANC visit. Data from meta-analysis of 6 trials shows that adding a 3rd and 4th dose improves birth weight in HIV-negative women (Kayentao et al. Unpublished data). Similarly, a recent study in Mali comparing the efficacy and safety of a 3-dose vs. 2-dose IPTp regimen has demonstrated the superiority of the 3-dose regimen in reducing the prevalence of placental parasitaemia (8% vs. 16.7%) and low birth weight (6.6% vs. 3.3%) or preterm birth (3.2% vs. 3.9%), again showing that the 2-dose regimen may not have been the optimal dose (Maiga et al, 2011).

**What next-important issues for Kenya**

**New drugs for IPTp**

The recent data on *P. falciparum* resistance to SP necessitates search for alternative drug or drug combinations for IPTp. Initially treatment effect was considered an important attribute for prevention and studies were designed to assess the efficacy of short *versus* long-acting drugs for example studies done on intermittent preventive treatment for malaria in infants (IPTi), one comparing chlorproguanil-dapsone (CD) vs. sulfadoxine-pyrimethamine (SP) vs. Amodiaquine (AQ) (Odhiambo et al, 2010) and another comparing chlorproguanil dapsone (CD), SP and mefloquine (MQ) (Gosling et al, 2009). These studies showed that long acting drugs are more effective than CD for which effect was not sustained beyond the window of pharmacological
protection (no lasting prophylactic effect); short acting drugs provide little (if any) benefit and therefore drugs with protracted suppressive activity are needed for malaria prevention (ter Kuile, personal communication). Potential alternative drugs include 1) artemether lumefantrine (although this may be just too short-acting), 2) amodiaquine (effective but not as well-tolerated as SP), 3) mefloquine monotherapy (effective but poor tolerability profile, currently being assessed for safety, efficacy and tolerability), 4) chloroquine-azithromycin (currently being assessed) and pyronaridine (currently no data in pregnancy), 5) piperaquine, in combination with dihydroartemisinin (DHA-PQ or DP) (currently being assessed). New drugs undergoing trials for IPTp include mefloquine currently undergoing a multicentre trial in five African countries of Kenya, Mozambique, Benin, Gabon and Tanzania (http://www.mip-consortium.org/), results are expected around 2012; chloroquine-azithromycin (being assessed in 5 African countries, results are expected by 2013; SP-azithromycin is studied in Papua new Guinea, results are expected by 2012, and IPTp with dihydroartemisinin-piperaquine (DHA-PQ) is assessed in Kenya and Indonesia.

Mefloquine has been shown to be one of the leading candidates. A study in Benin showed that mefloquine was more efficacious than SP in preventing placental malaria, clinical malaria and maternal anaemia at delivery (Briand et al, 2009). However, of the available combinations DP remains the most attractive. DP is better tolerated than AQ-AS, and because of the long half-life of piperaquine of about 23 days (19-28 days in adults and 14 days (10-18) days in children (Kamya, 2007; Zongo et al, 2007), it has been shown to provide longer post-treatment prophylaxis than artemether-lumefantrine or amodiaquine-artesunate by one or two weeks after each dose.

PQ in combination with dihydroartemisinin (DHA) has also been shown to be highly efficacious (> 98% cure rates, even after prolonged follow up of 42-56 days) in non-pregnant populations (Denis et al, 2002; Smithuis et al, 2006).

**Alternative strategies to replace IPTp**

*Intermittent screening and treatment in pregnancy (ISTp)*

Another strategy which is quickly gaining recognition is the ISTp. The 1990’s recorded a significant decline in malaria incidence in sub-Saharan Africa (Omrera et al, 2010; Feng et al, 2010) and although this decline is not universal (Okuro et al, 2010), there is substantial evidence
that increased coverage with malaria control interventions, especially with ITNs and targeted IRS, have been the leading contributors to this decline (Steketee & Campbell, 2010). With the increased coverage with these strategies malaria incidence is expected to reduce even further. Under these conditions the malaria control community will have to adopt the most cost-effective strategies. In pregnant women for example, focus may change from IPTp to either using intermittent screening and treatment of those being positive (ISTp) or chemoprevention with a long acting drug. This alternative strategy of intermittent screening and treatment (ISTp) involves increased screening at the time of focused antenatal care (FANC), essentially screening with RDTs (three or four times in the second and third trimester) as part of FANC then treat RDT-positive cases with a long-acting ACT anti-malarial drug. Adoption of ISTp will necessitate a shift from presumptive treatment to better diagnostics such as RDTs which are cheap and easy to use at the point of care.

*Malaria control in the context of reduced transmission or elimination*

The declining burden of malaria is expected to diminish the role of IPTp-SP especially in countries where prevalence has been drastically reduced or where malaria has been eliminated (White et al, 2008). In this context, it will become more cost-effective to screen pregnant women and to treat only those who are positive for malaria (Tagbor et al, 2010). More attention will be paid to finding alternative strategies to IPTp-SP or chemoprevention with long-acting drugs and to assess the risk-benefit ratio of potential replacement strategy to IPTp-SP; it will become more practical to screen and treat only those who have malaria parasites. The perceived advantage of IST is that it will limit drug exposure to those who need it, reduce overtreatment and reduce drug pressure, the downside being that it is more complicated, expensive and has the inherent risk of missing sub-patient infections. Studies comparing ISTp and IPTp-SP are currently underway in different geographic and epidemiological zones (West Africa, Malawi, India, Indonesia, and Kenya) and results are expected around 2013. The results of a recent study in Ghana investigating whether IST is as effective and as safe as IPTp concluded that in an area of moderately high transmission IST with SP or AS+AQ may be a safe and effective strategy for the control of malaria in pregnancy (Tagbor et al, 2010).
Predictions for MIP control in Africa (2012-2015)

Improvements with widespread use of ACTs in the second and third trimester of pregnancy and use of RDTs are expected in this period. Long lasting insecticide treated nets will remain a key component but IPTp is expected to be modified in different areas. Depending on changes in transmission and resistance the uniform strategies that have been applied so far will probably be replaced by strategies adapted to the regional (local) situation. In areas of low to moderate SP resistance such as parts of West Africa IPTp-SP may continue to be used widely, but ensuring 3+ regimens. ISTp may be introduced in very low transmission areas. In areas of high SP resistance (East and Southern Africa), IPTp-SP should gradually be replaced by other drug combinations. IPTp-MQ/ISTp may be continued in some countries.

Malaria in pregnancy control in Africa 2015-20

If further sustained reduction of malaria transmission will occur, building up of immunity (premonition) in the population may be impaired and more symptomatic malaria may occur in pregnant women with more preterm LBW and more pregnancy loss. ISTp or new IPTp drugs with an ITN will be used for malaria prevention (no fixed dose combination of IPTp) and perhaps a vaccine aimed at malaria in pregnancy may be developed.

Conclusions and recommendations

Major gains for malaria control during pregnancy have been threatened by the rapid development of SP resistance, necessitating a shift to other available drugs and evaluation of these drugs for safety in pregnancy, development of new drugs or new approaches. Coverage by strategies that were thought to be easy to implement such as IPTp-SP remains low and novel ways are needed to overcome these short-comings. Major suggestions include better integration with ANC, refresher training for health care providers, integrating simplified messages to supplement key policy documents (which are often unavailable at the point of use or too large to read) and early engagement with policy makers in research endeavours. In Kenya for example, it is unbelievable that it has now taken almost five years to change from 5mg folic acid to the internationally recommended doses of 0.4-0.6 mg, despite the availability of evidence and the fact that folic acid deficiency is not common in this population.
Changes of policies take too long; workers in the field should press authorities to be more active. Change of SP by a more effective drug will soon be necessary, may in fact already be overdue. Those who attend to the pregnant women should take the lead in these decisions.

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